

Human T-Lymphotropic Virus Type I (HTLV-I) and Tropical Spastic Paraparesis or HTLV-I-Associated Myelopathy in Hawaii

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Tropical spastic paraparesis or human T-lymphotropic virus type I (HTLV-I)-associated myelopathy is a degenerative encephalomyelopathy with pyramidal tract dysfunction affecting the lower extremities. It is associated with HTLV-I infection and found primarily in the Caribbean region and in southwestern Japan. Five cases of tropical spastic paraparesis (or HTLV-I-associated myelopathy) in Hawaii are reported. All five patients were born in Hawaii; four are women. Each of the patients has parents who were from HTLV-I-endemic areas of Japan. Two of these patients had serum antibodies to HTLV-I. Five of six of the spouses and children of the seropositive patients were also seropositive. Viral cultures of lymphocytes from both seropositive patients and two of the three seropositive children were positive for HTLV-I. None of the five patients had a history of antecedent blood transfusion, multiple sexual partners, or intravenous drug use. There is no evidence of adult T-cell leukemia or lymphoma in any of the patients or their families. Given the increasing seroprevalence of HTLV-I in the United States, clinicians need to be alert to new cases of this disorder.

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Tropical spastic paraparesis (TSP) or human T-lymphotropic virus type I (HTLV-I)-associated myelopathy (HAM) is a slowly progressive encephalomyelopathy that generally presents in the middle adult years. The initial symptoms are increasing difficulty in walking, low back pain, and cramping sensations of the legs. Urinary sphincter dysfunction is also common. Impotence or diminished libido is almost universal. Most cases reach a clinical plateau within two years of the start of symptoms and remain at that level of function, without remission, for years.

Groups of patients with this disorder have long been recognized in southern India, Jamaica, South Africa, and Colombia.¹⁻⁴ The geographic clustering and sporadic appearance of this neurologic syndrome led to the finding of both epidemic and endemic forms of the disease. Epidemic forms followed increased ingestion of vegetable toxins in the context of malnutrition and regional drought.^{5,6} Clues to the origin of the endemic form remained unclear, however, until antibodies to HTLV-I were found in the blood of ten patients with TSP/HAM in Martinique.⁷ Seropositivity to HTLV-I was subsequently confirmed in a number of Jamaican and Colombian patients with the syndrome, and, in addition, antibodies to HTLV-I were found in their cerebrospinal fluid.⁸

Soon afterward, patients living in nontropical areas of southwestern Japan, which are endemic for HTLV-I and adult T-cell leukemia or lymphoma (ATLL), were independently reported to have the same chronic, slowly progressive spastic myelopathy. Serum from these patients was also positive for HTLV-I antibodies.⁹ This syndrome in Japan was termed "HTLV-I-associated myelopathy." Subsequently, cases of tropical spastic paraparesis or myelopathy associated with HTLV-I have been reported from Trinidad and Tobago,¹⁰ Ivory Coast,¹¹ Colombia,^{12,13} the Seychelles islands,¹⁴ West Indian-born residents in the United Kingdom,¹⁵ France,¹⁶ Italy,¹⁷ Peru,¹⁸ and from the United States.¹⁹

Pathologic evidence clearly linked the Caribbean form with the Japanese form of spastic paraparesis. The primary changes are astrocytic gliosis, capillary proliferation, perivascular lymphocyte cuffing, and loss of both myelin and axons in the pyramidal, spinocerebellar, and dorsal columns of the spinal cord. Similar but less striking changes are found in the medulla, pons, and in the white matter of the cerebellum and cerebrum of these patients.²⁰

Because of confusion over the nomenclature, a consensus panel at the 1989 World Health Organization HTLV-I meeting in Kagoshima, Japan, determined that the diseases,

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ABBREVIATIONS USED IN TEXT

ATLL = adult T-cell leukemia or lymphoma
 ELISA = enzyme-linked immunosorbent assay
 HAM = HTLV-I-associated myelopathy
 HIV = human immunodeficiency virus
 HTLV-I = human T-lymphotropic virus type I
 TSP = tropical spastic paraparesis

tropical spastic paraparesis and HTLV-I-associated myelopathy, are identical and formally proposed that the syndrome be called "TSP/HAM."²¹

Persuasive evidence for a closer association of disease and virus came with the isolation of HTLV-I from cerebrospinal fluid lymphocytes of a patient in Japan with TSP/HAM who had both serum and cerebrospinal fluid HTLV-I antibodies.²² Subsequent work using electron microscopy has shown HTLV-I-like viral particles in pathologic spinal cord tissue from a Jamaican patient with TSP/HAM.²³ Intact HTLV-I virus has been produced using peripheral lymphocytes from healthy controls cocultured with irradiated T-lymphocyte cell lines derived from patients with TSP/HAM.²⁴ Southern blot hybridization of cultured T lymphocytes from cerebrospinal fluid of patients with TSP/HAM has revealed HTLV-I in a proviral form in these cells. Electron microscopy has shown type C retroviral particles in the same cultured cells.²⁵ Intrathecal synthesis of HTLV-I antibodies and oligoclonal bands in cerebrospinal fluid specimens of TSP/HAM patients from the Caribbean region and West Africa has also strengthened the evidence for the causal relationship between HTLV-I and TSP/HAM.²⁶

At the molecular level, specific DNA sequences of HTLV-I isolated from patients with HTLV-I-associated myelopathy were found to be homologous on DNA blotting to sequences from patients with adult T-cell leukemia or lymphoma.²⁷ Atypical lymphocytes with lobulated nuclei similar to the atypical lymphocytes in the blood of patients with ATLL are found in the peripheral blood and cerebrospinal fluid of patients with TSP/HAM.²⁸ To date, only one patient has been reported who had both HTLV-I-associated diseases: he was a Trinidadian man who had TSP/HAM for 16 years before adult T-cell lymphoma developed.¹⁰

Evidence for HTLV-I transmission points to three primary routes: sexual transmission, most frequently from male to female through the leukocyte component of semen^{13,29,30}; mother-to-infant transmission through breast milk^{29,31,32}; and direct transmission by blood transfusion³³⁻³⁷ as well as by sharing needles in intravenous drug use.³⁸ Although lymphocytes containing HTLV-I have been found in the umbilical cord blood of a baby born of an HTLV-I-positive mother, in utero transmission is unusual.³⁹ Data from Okinawan residents, Okinawan immigrants to Hawaii, and their Hawaiian-born offspring implicate the importance of intimate household contact (sexual as well as breast-feeding routes) in the transmission of this virus.⁴⁰ The transmission of HTLV-I differs from that of the human immunodeficiency virus (HIV) in that for HTLV-I to be transmitted, it must be in an intracellular form. Recipients of lyophilized factor concentrates did not seroconvert to HTLV-I as they did to HIV.⁴¹

The possibility that mosquitoes or other hematophagous insects may be HTLV-I vectors is unlikely but is still unresolved.^{42,43} The role of cofactor parasites is also uncer-

tain.^{42,44} Environmental antigenic stimulation, parasitic or otherwise, has been proposed as a mechanism of activation of latently infected helper T lymphocytes or proviral states (including "smoldering ATLL") which then may develop into clinical TSP/HAM or ATLL.^{40,42}

It is not clear why most antibody-positive persons remain asymptomatic while in a few TSP/HAM (or ATLL) develops. Recent evidence from human leukocyte antigen screening of HTLV-I-endemic areas in Japan indicates that there is a relationship between specific HLA haplotypes and persons in whom either TSP/HAM or ATLL develops, suggesting genetically determined HTLV-I disease susceptibility.⁴⁵

Antibodies to HTLV-I are present at a rate of 0.2% in the healthy, volunteer blood donor population in Hawaii (J. Frohlich, MD, Blood Bank of Hawaii, oral communication, February 1989). Adult T-cell leukemia or lymphoma associated with HTLV-I serum antibodies has been reported in Hawaii,^{46,47} but heretofore not TSP/HAM.

Given the presence of ATLL and the background level of HTLV-I seropositivity, we postulated that TSP/HAM was present in Hawaii and that it would be associated with HTLV-I infection.

Patients and Methods

Patients

From a survey of four neurology practices in Honolulu, a group of patients with unexplained spastic myelopathy was selected. Five of these patients were found to have tropical spastic paraparesis or HTLV-I-associated myelopathy on the basis of an interview, neurologic examination, and a review of their medical records. Criteria for TSP/HAM in this study are a slowly progressive clinical course reaching a steady state of neurologic impairment over one to two years and having no remissions, primary pyramidal tract signs including bilateral lower extremity weakness and spasticity, no evidence of other neurologic disease (including dementia), and no myelographic evidence of spinal cord compression.⁴⁸⁻⁵⁰ There was no history of blood transfusions, intravenous drug use, or homosexual or nonmonogamous heterosexual activity in any of the patients found to have TSP/HAM or in their family members.

Volunteer blood donors at the Blood Bank of Hawaii were used as a control population to determine the background rate of HTLV-I seroprevalence in this area. Because all five patients with TSP/HAM are of Japanese descent and because specific areas of Japan have high rates of HTLV-I seropositivity, only serum from Hawaiian blood donors of Japanese ancestry was used to more closely match the patients reported in this study. The rate of overall HTLV-I seropositivity in blood donors in Hawaii is 0.2%. The rate of HTLV-I seropositivity in blood donors of Japanese descent in Hawaii is 0.8% (J. Frohlich, MD, Blood Bank of Hawaii, oral communication, February 1989).

Laboratory Tests

A complete blood count was done on each patient with TSP/HAM. Serum specimens from each of the patients and 17 of their immediate family members or close relatives were tested in duplicate using the Biotech/Dupont HTLV-I enzyme-linked immunosorbent assay (ELISA) kit (Wilmington, Delaware). This kit uses detergent-disrupted

HTLV-I virions produced in a HuT-102-2B T-lymphocyte cell line. Positivity was determined by establishing a cutoff absorbance value (at 410 nm). The cutoff was set at 60% of the mean absorbance of three positive control serum specimens. Any specimen whose average absorbance was greater than the cutoff was deemed positive.⁵¹

All ELISA-positive results and ELISA-negative results on serum specimens of TSP/HAM patients were confirmed by Western blot. The Biotech Western blot test kit (Rockville, Maryland) for HTLV-I was used. This kit uses nitrocellulose strips onto which HTLV-I-specific polypeptides have been electrophoretically blotted. Specifically bound human immunoglobulins to HTLV-I antigens such as p19, p24, p28, p36, and gp46 are visualized by a goat antihuman immunoglobulin biotin conjugate and an avidin horseradish peroxidase conjugate with 4-chloro-1-naphthol substrate. The presence of HTLV-I antibodies in a patient's serum is indicated by *in situ* bands representing specific HTLV-I antigens. Serum that was reactive with both p19 and p24 was considered to contain HTLV-I antibodies.

All patients with ELISA-positive serum and their seropositive family members were tested for culturable HTLV-I virus. Heparinized peripheral blood leukocytes from these persons were banded in a solution of Ficoll and diatrizoate (Hypaque) and stimulated with phytohemagglutinin P at 5 µg per ml for two to four days. The mitogen was then removed and the cells cocultivated for as long as ten weeks with an equal number of phytohemagglutinin-stimulated mononuclear cells from human umbilical cords. Culturing was done in RPMI 1640 with a 20% solution of heat-inactivated fetal bovine serum and 10% interleukin-2 (Cellular Products, Buffalo, New York). Periodically, fresh cord blood cells were added when necessary to maintain a culture. Several times during the cocultivation process, cells were placed on slides, fixed with a 1:1 solution of methanol and acetone, and tested for the expression of HTLV-I p19 and p24 by reaction with monoclonal antibodies specific for those antigens. The reaction of the antibodies with the cells was detected by the alkaline phosphatase, antialkaline phosphatase immunocytochemical procedure.

Results

Five Hawaiian patients were found to meet the clinical criteria for tropical spastic paraparesis or HTLV-I-associated myelopathy. Each of these patients was born in Hawaii and has lived there for his or her entire life. The parents of these patients were all born in Japan. Each parent emigrated to Hawaii before age 20 and before marriage. Four patients are married women and one is a single man. There is no history of an antecedent blood transfusion, intravenous drug use, or multiple sexual partners in any of the patients. All of the patients were breast-fed as infants. They range in age from 46 to 71 years (mean, 58.4 years). The age at which symptoms first started ranges from 36 to 52 years (mean, 41.6 years). Symptoms have lasted from 7 to 32 years (mean, 16.8 years) in the five patients.

The first symptom of clinical disease in each of these patients was leg weakness, most noticeable as difficulty going down stairs and early fatigue on walking distances. Other early symptoms in this patient group were lower extremity dysesthesias and muscle spasms. As the disease progressed, patients reported increasing awkwardness of their

gait and, later, falling due to leg weakness. Several reported difficulty in getting out of bed in the morning because of "muscle stiffness." All five patients had urinary incontinence of a variable degree. There has been no remission of signs or symptoms in any of these patients. None of these patients has any intellectual impairment. The present degree of physical disability ranges from needing a cane for ambulation (two patients), to requiring a walker (two patients), to being completely wheelchair bound (one patient). Three have had hip fractures following falling.

None of the patients has any evidence of upper extremity involvement by examination. Two patients do, however, have upper extremity dysesthesias. All patients have hyperreflexic knee and ankle jerks with extensor plantar reflexes bilaterally. Three have clonus at the ankle. Quadriceps and hamstring muscle tone shows considerable spasticity but is fairly symmetric in all patients. All patients have a variable degree of weakness in the lower extremities, with the anterior tibialis muscle group being most affected. Sensation to temperature and pinprick is normal in all patients. Three patients have decreased vibratory sensation at the level of the metatarsals. Examination of the gait shows a mild to moderate foot drop, difficulty lifting the knees, and pronounced scissoring (one patient was unable to ambulate). Gait rhythmicity was irregular. Stopping and turning required more effort and concentration than normal. Cerebellar function was intact in the upper extremities in all patients: it was difficult to assess in the lower extremities because of spasticity and weakness. Other neurologic findings are summarized in Table 1. Myelograms of each of the five patients were normal. Hemoglobin concentrations, hematocrits, and leukocyte and differential cell counts were normal in all patients. A VDRL test for syphilis was negative in all patients.

There was no significant difference clinically between the seropositive and the seronegative patients. The seropositive patients were neither the most nor the least seriously affected of the five patients with tropical spastic paraparesis.

The only medications taken frequently by several of these patients were muscle relaxants, which were used on a symptomatic basis. Antihypertensive and thyroid supplement medication were each taken by one patient in this group. None of the patients had ever been treated with steroid, immunosuppressive, or immunomodulatory medications.

Two of the five patients with TSP/HAM are HTLV-I antibody-positive. The serologic results from the five patients and their relatives are presented in Figure 1. The results of Western blot confirmation of the ELISA-positive persons are shown in Figure 2. In each case, the Western blot test confirmed the result of the ELISA tests done on these seropositive patients. Western blot tests on the seronegative patients were negative for all bands.

Antibody titers are shown in Table 2. There is excellent serologic correlation among the three HTLV-I-negative patients (patients 1, 2, and 3) and their family members: all spouses, siblings, and offspring tested are seronegative. All three of the seronegative patients had parents who were born in HTLV-I-endemic areas of Japan.

The correlation among the two seropositive patients (patients 4 and 5) and their families is nearly as strong. Each of the spouses is seropositive. Three of the four offspring tested are also seropositive. (A single offspring was unavailable for testing.) The 82-year-old mother of patient 4—born in an

endemic area of Japan and immigrated to Hawaii at 16 years of age—is seronegative. Four of ten living siblings of patients were tested, and one of these is seropositive. Although not examined, the seropositive sibling (female) reported progressive leg weakness and gait instability. The spouse of that seropositive sibling is seronegative.

Figure 3 shows the results of HTLV-I viral cultures using peripheral lymphocytes from the seropositive patients with TSP/HAM and their seropositive family members. Patient 4 and her two seropositive offspring are culture-positive. Her spouse, who is also seropositive, is culture-negative. Patient 5 is culture-positive for HTLV-I. Both her seropositive spouse and her seropositive offspring are culture-negative. As a negative control, lymphocytes from patient 3 (seronegative) were cultured using the same methods; he was culture-negative for HTLV-I.

Activated, ATLL-like, atypical lymphocytes with polylobulated, cerebriform nuclei were seen on the peripheral

smears of both seropositive patients (Figure 4). The spouse of patient 5 also had ATLL-like lymphocytes on his peripheral smear. In patient 5, polylobulated nuclei are present in approximately 10% of her peripheral lymphocytes. In the other two persons, similar nuclei were seen in fewer than 5% of the lymphocytes on their peripheral smears.

Discussion

These data indicate that tropical spastic paraparesis, or HTLV-I-associated myelopathy, a neurologic syndrome found in many areas of the world, is present in Hawaii. Unique to this location are the elements of tropical spastic paraparesis found in the Caribbean region and of HTLV-I-associated myelopathy in southwestern Japan. Hawaiian TSP/HAM exists in a tropical environment (unlike in Japan), but in Hawaii it is found in the immediate descendants of Japanese migrants from HTLV-I-endemic areas (in the pattern of Japanese familial transmission). There is no differ-

TABLE 1.—Clinical Summary of Patients With Tropical Spastic Paraparesis

Patient	Age, Sex yrs	HTLV-I Serologic Results	Symptoms				Neurologic Signs			
			Age at Onset, yrs	Early	Later	Bladder	Vibratory at Toes	Knee Reflexes	Ankle Reflexes	Gait
1	... 68 ♀	Neg	36	Leg stiffness; spasms	Dysesthesias; falling	Incontinence	Decreased	Hyperreactive	Clonus	Stiff, awkward; foot drop; scissoring; requires walker
2	... 46 ♀	Neg	39	Leg weakness	Low-back aches	Frequency	Normal	Increased	Clonus	Stiff; foot drop; scissoring; requires cane
3	... 48 ♂	Neg	38	Leg weakness; unsteady gait	Leg cramps, spasms; dysesthesias, falling	Incontinence	Decreased	Hyperreactive	None	Unable to stand; contractures; wheelchair bound
4	... 59 ♀	Pos	52	Leg weakness; unsteady gait	Low-back pains; leg cramps	Incontinence	Normal	Increased	Hyperreactive	Awkward; foot drop; mild scissoring; requires cane
5	... 71 ♀	Pos	43	Leg weakness, aches	Wavering gait; leg cramps	Incontinence	Decreased	Hyperreactive	Clonus	Stiff, halting; foot drop; scissoring; requires walker
HTLV-I=human T-lymphotropic virus type I, Neg=negative, Pos=positive										

HTLV-I=human T-lymphotropic virus type I, Neg=negative, Pos=positive

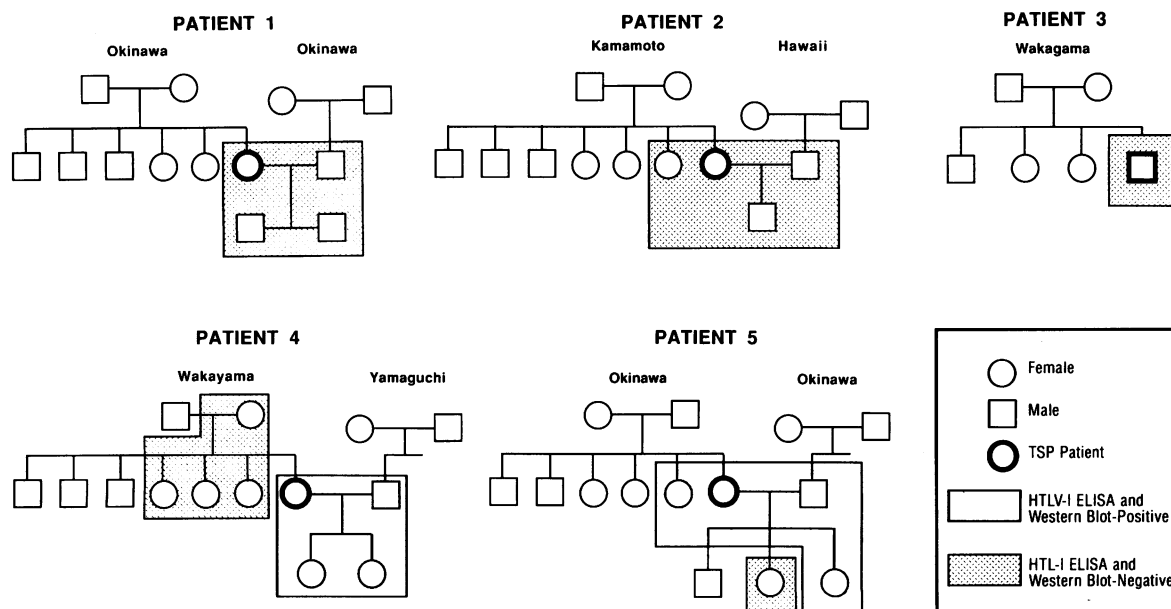


Figure 1.—The pedigree chart shows the city or state of birth and the distribution of the human T-lymphotropic virus type I (HTLV-I) in the families of the patients with tropical spastic paraparesis (TSP). ELISA = enzyme-linked immunosorbent assay

ence in the signs, symptoms, or prognosis between these two syndromes; they are the same disease.²¹ Postmortem pathologic evidence bears out these similarities.²⁰ Neither name is optimal because patients with this disease are found in nontropical areas (southwestern Japan) and not all patients with the clinical disease are seropositive (which is a requirement of HAM in Japan); thus, "TSP/HAM" is a good compromise.

The familial virus clustering pattern reported in highly endemic areas is present in the seropositive families described here. Viral clustering of HTLV-I, as found in Hawaii, includes parents and their children. Parental siblings living in other households, however, do not share the same high rate of seropositivity as do household members.

These data do not pinpoint specific modes of transmission in Hawaii, but they indicate the importance of close familial contact in viral transmission. Both vertical and horizontal routes of transmission, common to other HTLV-I-endemic areas, probably occurred in the families described in this report. In the case of patient 5, transmission may have been either vertical, through breast milk from her mother (from an endemic area), or horizontal, through male-to-female sexual transmission from her seropositive spouse who has a very high antibody titer and whose parents are also from an HTLV-I-endemic area. If the latter is the case, this may explain why the eldest offspring of this family is seronegative: at the time of the birth of this first child, patient 5 may

not have been infected with HTLV-I or, if infected, she may not have had a high enough viral titer at that time to effectively transmit HTLV-I to her first infant.

In the case of patient 4, whose parents are from an endemic area but whose spouse's parents are from an area of low seroprevalence in Japan, the transmission of virus to both children was most likely through breast milk. The spouse of patient 4, who had a low antibody titer, may have been exposed to the virus through female-to-male sexual transmission from his seropositive wife. This is an uncommon route of HTLV-I transmission in Japan, although it may be analogous to the female-to-male transmission of HIV type 1 seen in other areas of the world. It is also possible that even though his mother was from an area of low seroprevalence, she was HTLV-I-positive and he was infected by the breast-milk route.

Three of our patients were seronegative. Approximately one of four TSP/HAM patients in the Caribbean region is seronegative, but few Japanese patients having the full clinical syndrome are seronegative (M. Osame, MD, Kago-

TABLE 2.—Human T-Cell Lymphotropic Virus Type I Antibody Titers in Seropositive Families

Patient and Family Member	Results of ELISA and Western Blot Tests	Antibody Titer	Virus Culture
Patient 4	Pos	1:2,560	Pos
Spouse	Pos	1:320	Neg
Offspring	Pos	1:640	Pos
Offspring	Pos	1:640	Pos
Patient 5	Pos	1:2,560	Pos
Spouse	Pos	1:20,480	Neg
Offspring	Pos	1:80	Neg

ELISA=enzyme-linked immunosorbent assay, Neg=negative, Pos=positive

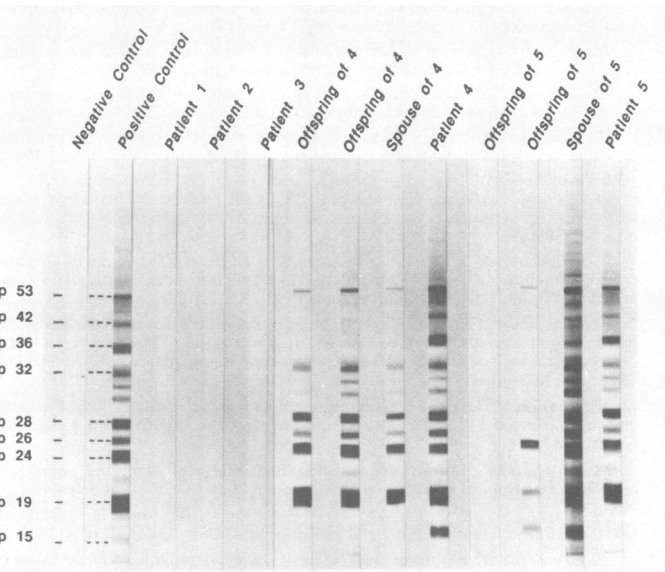
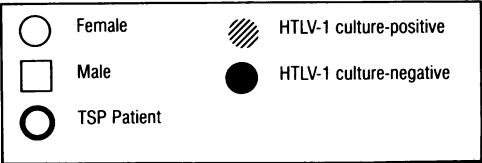
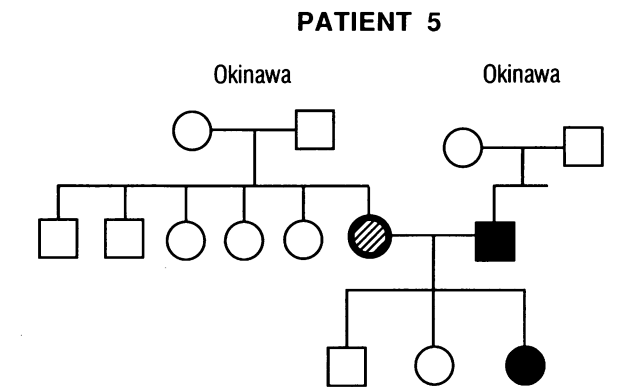
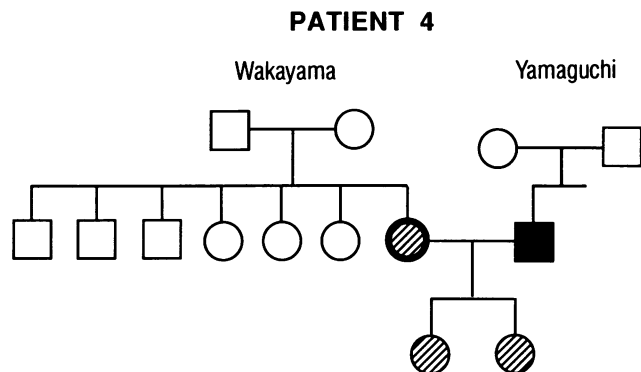


Figure 2.—The Western blot results are shown for the patients with tropical spastic paraparesis and their seropositive family members.

Figure 3.—The charts show the results of the cultures for human T-lymphotropic virus type I (HTLV-I) in patients 4 and 5 and their siblings and spouses. TSP = tropical spastic paraparesis

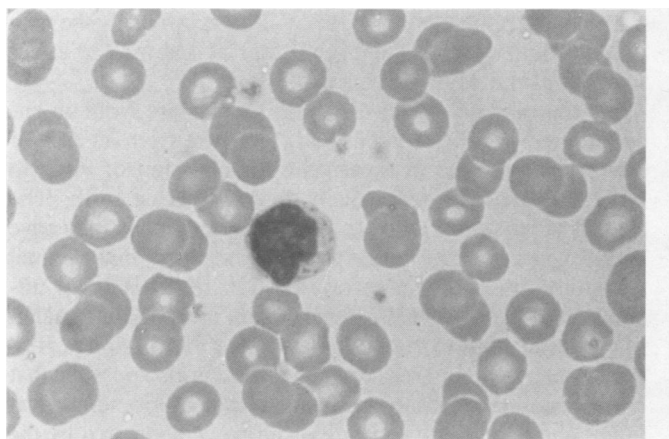


Figure 4.—A representative atypical lymphocyte is seen on the peripheral blood smear of patient 5 (Wright's stain, original magnification $\times 1,000$).

shima, Japan, oral communication, February 1989). In a recent study, only two of eight patients with TSP/HAM from the United States were found to have antibodies to HTLV-I.¹⁹ It may be that, in seronegative patients, the virus is present but serologically silent in a proviral form. It will be important to study seronegative patients with TSP/HAM for HTLV-I infection using more sensitive techniques including the polymerase chain reaction and more extensive attempts at viral culture. It may also be that a second virus may cause a clinically similar disease.

These cases of TSP/HAM are among the first described in citizens of the United States. Both TSP/HAM and ATLL represent patterns of HTLV-I disease not commonly seen in this country. With the increasing prevalence of HTLV-I noted in intravenous drug users in this country and with the finding of patients with leukemia who seroconverted following multiple blood transfusions in New York City,⁵² there is reason to anticipate that TSP/HAM will develop in some of the recipients of these blood transfusions in endemic regions of the US. In addition to transfusion recipients, intravenous drug users, their sexual partners, and their breast-fed infants are other groups at risk of having TSP/HAM. As seen in Hawaii, persons whose parents emigrated to the US from HTLV-I-endemic areas are also clearly at risk of TSP/HAM or ATLL developing. To date there are no reports of cases of ATLL in Japan or in the US that have resulted from transfusion.⁵³ Given the long latency between HTLV-I infection and the development of ATLL, transfusion-associated ATLL will be difficult to identify.

To protect the US blood supply and the noninfected, recipient population as a whole, epidemiologic information needs to be obtained to determine which areas and which subgroups in the United States have the highest rates of HTLV-I infection. Routine screening of donor blood in these areas will limit iatrogenic HTLV-I transmission and reduce the rate at which HTLV-I is introduced to this country.

Because of the particularly long latency period of HTLV-I infection, the potential scope of this problem is difficult to assess in the absence of seroprevalence information at the national level. An additional factor in estimating the magnitude of possible clinical disease is the question of whether those persons infected with both HIV and HTLV-I will be more likely to have TSP/HAM or ATLL or whether immuno-

deficiency will develop and they will succumb to the acquired immunodeficiency syndrome first. Clinicians need to be aware of TSP/HAM in patients presenting with spastic paraparesis and that TSP/HAM provides a different model for the study of retroviral infection of the central nervous system.

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